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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ---	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/15135	International filing date (day/month/year) 02/07/1999	Priority date (day/month/year) 02/07/1998
International Patent Classification (IPC) or national classification and IPC C12N15/10		
Applicant RESEARCH AND DEVELOPMENT INSTITUTE, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 29/01/2000	Date of completion of this report 21.09.2000
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I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-51 as originally filed

Claims, No.:

1-11 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
 - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

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Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 4-11
	No:	Claims	2, 3
Inventive step (IS)	Yes:	Claims	4-11
	No:	Claims	1-3
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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EXAMINATION REPORT - SEPARATE SHEET**

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Re Item I

Basis of the report

The examination is being carried out on the following application documents:

Text for the Contracting States:

AT BE CH DE DK ES FI FR GB GR IT IE LI LU MC NL PT SE

Description, pages:

1-51 as originally filed

Claims, No.:

1-11 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

Re Item II

Priority

The priority documents pertaining to the present application were not available at the time of establishing this International Preliminary Examination Report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D1 (see below) cited in the International Search Report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

D1: LONG D.M. ET AL.: 'In vivo addition of telomeric repeats to foreign DNA generates extrachromosomal DNAs in the taxol-producing fungus *Pestalotiopsis microspora*' FUNGAL GENET. BIOL., vol. 24, no. 3, August 1998 (1998-08), pages 335-344

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Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D2: WO 97 38571 A (UNIV WASHINGTON) 23 October 1997 (1997-10-23)
- D3: National Science Foundation, Grant No. 9724999, 1.7.1997-30.6.1998 Long D.M. & Strobel G.A., 'SGER: efficient extrachromosomal replication of exogenous DNA by a filamentous fungus'. <http://fundedresearch.cos.com/cgi-bin/NSF/getRec?9724999>, cited in the application
- D4: STROBEL ET AL: 'Taxol from Pestalotiopsis microspora, an endophytic fungus of Taxus wallachiana' MICROBIOLOGY, vol. 142, no. 142, 1996, page 435-440-440 ISSN: 1350-0872, cited in the application

The present application relates to methods for the production of extrachromosomal replicable nucleic acids by introduction into Pestalotiopsis cells as well as to artificial chromosomes.

1. Novelty (Article 33(2) PCT):

The subject-matter of claims 2 and 3 is anticipated by document D3. Claim 2 relates to the generation of extrachromosomal DNA by introducing DNA into a Pestalotiopsis cell, and claim 3 relates to the generation of replicable nucleic acid elements by introducing DNA into Pestalotiopsis cells. D3 discloses that Pestalotiopsis microspora has the unique ability to convert non-replicating DNA introduced into the cell into self-replicating plasmids. It is stated that this organism, in contrast to other filamentous fungi, does not replicate foreign DNA through integration into the chromosome, i.e. that the foreign DNA is extrachromosomal.

2. Inventive step (Article 33(3) PCT):

Claims 1-3 lack an inventive step in the sense of Article 33(3) PCT in view of document D3. As outlined in paragraph 1 (see above), claims 2 and 3 relate to the production of extrachromosomal and replicable nucleic acids in Pestalotiopsis. That this organism is

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able to convert foreign DNA into extrachromosomal and replicable plasmids has been disclosed in D3. This general principle works for all kinds of DNA, so that it is not of relevance which DNA is introduced into the fungal cell. In view of D3 claims 2 and 3 thus cannot be considered inventive. That *Pestalotiopsis* tolerates and even produces taxol has been disclosed in D4.

a) In view of D3 the subject-matter of claim 1 has been disclosed, although the exact mode of action was not known at that point.

Inventive activity in the sense of Article 33(3) PCT cannot be acknowledged for a claim relating to a known method which differs from the state of the art merely by the indication of the scientific principles underlying this method.

b) Even if novelty of claims 2 and 3 was restored, both claims would not be considered to involve an inventive step in the sense of Article 33(3) PCT for the same reasoning as outlined above.

3. Claims 4-11 are considered to fulfil the criteria set forth in Article 33(1) PCT concerning novelty and inventive step.

Re Item VIII

Certain observations on the international application

The present application lacks clarity (Article 6 PCT) and support from the description (Article 5 PCT):

1. Claim 5 requires the DNA of claims 1-4 to have at least 80% similarity to *Pestalotiopsis* DNA. However, it is not clear whether this refers to the whole genome or to specific genes of *Pestalotiopsis*. In case that it refers to particular genes, these have to be identified and their nature (e.g. the amino acid or nucleotide sequence) has to be known. Otherwise the claim would be purely speculative.
2. The subject-matter of claim 6 is not fully supported in the description. At present, taxol production is known from certain yew trees (see D2, page 4) and from certain fungi such as *Pestalotiopsis*. As outlined in the description of the

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application, the biosynthetic pathway of taxol production is not known in detail for the fungi, and in the case of the plant taxol production only one enzyme (i.e. taxadiene synthase) has been both identified and cloned. It is possible that in the future further organisms will be identified which produce taxol. As at present there is no information which organisms this might be, claim 6 lacks support and is insufficiently disclosed (Article 5 PCT).

3. The methods of claims 1-4 require the introduction of DNA into a *Pestalotiopsis* cell. However, it is not stated in the description that the DNA sequences for the enzymes referred to in claim 7 are known. Taxadiene synthase is known from *Taxus brevifolia*, but at least the taxadiene-5-hydroxylase DNA sequence at present is not known. The subject-matter of claim 7 therefore is insufficiently disclosed (Article 5 PCT).
4. Claim 11 relates to an artificial chromosome comprising a *Pestalotiopsis* telomerase and a DNA involved in taxol production.
 - a) Neither a *Pestalotiopsis* telomerase nor its subunit have been disclosed. The description of the present application does not disclose the DNA sequence or any other characterising feature of the enzyme, and concerning the other enzymes mentioned in the claim the objections raised in paragraph 3. (see above) are valid. Claim 11 therefore lacks support from the description.
 - b) In view of the relationship between claims 1-10 and claim 11 the present application does not fulfil the requirements of Rule 13 PCT concerning unity. Claims 1-4 and those claims dependent on them relate to methods for the production of extrachromosomal and replicable nucleic acid sequences. The subject-matter of claim 11 is not linked with the other claims by any special technical effect or by a certain feature. The telomerase of claim 11 is not present in claims 1-10, and the enzymes involved in the taxol production referred to in claim 11 do not necessarily have to be the same as those referred to in claims 1-4.